REMARKS

Claims 1, 3-5, 19-34, and 37-40 are pending in the present application. Among them, Claims 3, 28, and 29 are directed to non-elected species, and are withdrawn from further consideration. Applicants have made minor clarifying amendments to claims 20, 25, 26 and 27, as discussed below.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Objection

The Examiner has objected to claims 4 and 24 for the recitation of "selected from among:--", and asserts that the claims should be amended to recite "selected from the group consisting of...". Applicants respectfully traverse.

Recitation of "the group consisting of..." is often used for Markush claims. However, such language is not required. MPEP 2173.05(h). Accordingly, Applicants request reconsideration and withdrawal of this objection.

Claim Rejections under 35 U.S.C. § 112, 2nd paragraph

Claims 1, 4-5, 19-27, 30-34 and 37-40 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Claims 1 and 4-5, 19-27, 30-34, 37-40 (which depend from claim 1) are rejected due to recitation of "address site" in claim 1 because the Examiner asserts that the term "address site" is allegedly unclear. Applicants respectfully traverse the rejection. The term "address site" and the use of this term is well-characterized throughout the specification, for example, in paragraphs [0107] and [0201]:

> [0107] The targeting moiety (or "address") is a moiety capable of recognizing and reversibly binding to a pre-determined "address binding site" (also herein "address site"), such as, for example, a soluble or membrane-bound biomolecules, or a component of a biomolecular accretion (e.g., a plaque or other insoluble protein-containing aggregate).
>
> [0201] It will be appreciated that a wide range of entities can be used as targeting moieties in the subject adzymes. Fundamentally, the targeting moiety reversibly binds to a pre-determined feature ("address site") associated with the targeted substrate. The targeting moiety presents one or more surfaces having chemical characteristics (e.g., hydrophobic, steric and/or ionic) which permit it to bind selectively, or relatively selectively, with the address site. In many embodiments, the address will be a modular protein (including peptide) domain which is provided in association with the catalytic domain. For example, the targeting moiety can be an antibody, or a fragment of an antibody which retains the ability to bind to the address site. Accordingly, the targeting moiety can be derived from such antibody and antibody fragments as monoclonal antibodies, including Fab and $F(ab)_2$ fragments, single chain antibodies (scFv), diabodies, and even fragments including the variable regions of an antibody heavy or light chain that binds to the address site.

In view of the clear guidance provided in the specification, Applicants assert that the meaning of "address site" is clear and definite. One of skill in the art can readily understand the metes and bounds of the claimed invention.

Claim 1 is also rejected due to recitation of the phrase "resistant to cleavage by said protease domain". According to the Examiner, the term "resistant" is a term of degree, and it is unclear how much cleavage is required for the adzyme to be considered "resistant." Applicants respectfully traverse.

Page 110, line 32 to page 112, line 29 describe how autocatalysis disrupts the ability of the adzyme to act effectively on its target. These passages provide many embodiments of adzymes that decrease or prevent autoproteolysis. In view of the detailed description provided in the specification and the level and understanding of one of skill in the art, Applicants submit that one of skill can readily appreciate the metes and bounds of the claimed invention. This standard is consistent with that set forth in MPEP 2173.05(b) ("The fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite under 35 U.S.C. 112, second paragraph. *Seattle Box Co., v. Industrial Crating & Packing, Inc.*, 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984)"). The MPEP and Federal Circuit support the conclusion

that relative terminology is acceptable so long as one of ordinary skill in the art would understand what is claimed, in light of the specification. Such is the case here.

Claim 19 is rejected due to recitation of the phrase "extracellular polypeptide" because the Examiner asserts it is unclear how an "extracellular polypeptide" is different from "the polypeptide" as any isolated polypeptide could be considered an extracellular polypeptide because the isolation step would separate it from the cell in which it was made. Applicants respectfully traverse the rejection. Page 5, lines 3-7 of the specification relates to an extracellular polypeptide: "[i]n certain embodiments, the substrate is a diffusible extracellular molecule, and preferably an extracellular signaling molecule that may act on an extracellular or intracellular receptor to triggers receptor-mediated cellular signaling. Optionally, the extracellular signaling molecule is an extracellular polypeptide signaling molecule, such as an inflammatory cytokine. In a preferred embodiment, the substrate is an interleukin-l (e.g., IL-lα., IL-lβ or TNF-α. In certain embodiments, the substrate is a polypeptide hormone, a growth factor and/or a cytokine, especially an inflammatory cytokine." In other words, the term is used to distinguish polypeptides that are secreted from cells and function, at least in part, extracellularly from polypeptides that are not secreted. Thus, Applicants assert that the meaning of an "extracellular polypeptide" is clear and definite.

Applicants take this opportunity to make a few additional points regarding the Examiner's rejection of claims 1 and 19. Applicants note that the standard for evaluating compliance with § 112, second paragraph, "is whether the claim meets the threshold requirements of clarity and precision, not whether more suitable language or modes of expression are available." MPEP 2173.02. In fact, the Office directs Examiners to "allow claims which define the patentable subject matter with a reasonable degree of particularity and distinctness." *Id.* (Emphasis in the original).

This same portion of the MPEP provides detailed guidance for evaluating definiteness of claim language and specifically cautions against analyzing such language in a vacuum. Rather, claim language must always be analyzed in view of:

(A) The content of the particular application disclosure;
(B) The teachings of the prior art; and

(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

Moreover, Applicants note that the Federal Circuit uses a high threshold for concluding that a claim is indefinite. "The requirement to 'distinctly' claim means that the claim must have a meaning discernible to one of ordinary skill in the art when construed according to correct principles ... Only when a claim remains insolubly ambiguous without a discernible meaning after all reasonable attempts at construction must a court declare it indefinite." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1366, (Fed. Cir. 2004).

In view of the standards and guidance set forth in MPEP 2173.02 and articulated by the Federal Circuit, Applicants contend that claims 1 and 19 define the metes and bounds of the claimed subject matter with particularity. In the event that the Examiner elects to maintain this rejection, Applicants request that the Examiner articulate the facts supporting his conclusion. A conclusion that Applicants submit is contrary to the position of the Patent Office and the Courts with respect to evaluating compliance with 112, second paragraph.

Claim 20 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in the recitation of "the adzyme is resistant to autocatalyzed proteolysis at a concentration equal to-" because the Examiner asserts it does not further limit the subject matter of the claim from which it depends. Applicants respectfully traverse the rejection. Page 7, lines 26-29 describes features of catalytic domains, and states: "[r]egardless of the type of catalytic domain, it may be desirable that the adzyme be resistant to autocatalysis (e.g., inter- or intra-molecular reactions), particularly at an adzyme concentration that is about equal to the concentration of adzyme in a solution to be administered to a subject." This provides literal support for claim 20, and demonstrates that it **may** be desirable for the adzyme to be resistant to autocatalysis at an adzyme concentration that is equal to the concentration of adzyme to be administered. The permissive use of "may" indicates that it is also possible for the adzyme to be resistant at an adzyme concentration that is not equal to the concentration of adzyme to be administered. Thus, claim 20 limits the scope of claim 1, and is not indefinite.

Claim 20 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in the recitation of the phrase "resistant to autocatalyzed—", because the Examiner alleges that "resistant" is a term of degree, and the resulting claim does not set forth the metes and bounds of the desired patent protection. Applicants traverse. As described above, page 110, line 32 to page 112, line 29 describe how autocatalysis disrupts the ability of the adzyme to act effectively on its target, and describes many steps that may be taken to prevent autoproteolysis. Given the disclosure and the level of skill in the art, Applicants submit that one of skill would readily appreciate the metes and bounds of the claimed invention. As noted above, the fact that claim 20 describes the claimed invention using relative invention does not mean that the claim necessarily fails to comply with 35 U.S.C. § 112, second paragraph.

Claim 25 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in the recitation of "enzyme construct" and "polypeptide factor" as there is no antecedent basis for enzyme construct and polypeptide factor in Claim 21. Applicants have amended claim 25 to replace "enzyme construct" with "adzyme" and "polypeptide factor" with "substrate." Applicants' amendments are believed to obviate the rejection.

Claim 26 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite in the recitation of "polypeptide including an antigen binding site thereof." To expedite prosecution, Applicants have amended claim 26 to recite "polypeptide(s) including an antigen binding site of an antibody". Applicants' amendment is believed to obviate the rejection by clarifying the metes and bounds of claim 26.

Claim 27 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in the recitation of "targeting domain...consisting of monoclonal antibody, an Fab and $F(ab)_2$, an scFv..." Applicants apologize for this obvious clerical error. Applicants have amended claim 27 to correct this typographical error. Applicants' amendment to claim 27 is not related to patentability and does not alter the scope of the claim.

In view of the foregoing arguments and amendments, Applicants contend that the pending claims are fully compliant with 35 U.S.C. § 112, second paragraph. Reconsideration and withdrawal of this rejection are requested.

Claim Rejections under 35 U.S.C. § 103(a)

Claims 1, 4, 19-27, 30-34 and 37 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of the combined teachings of Davis et al (WO 00/64485, hereinafter "Davis") and Chamow et al. (Trend Biotech, 1996, 14. pp. 52-60, hereinafter "Chamow"). The Examiner asserts that Davis teaches fusion proteins that have greater catalytic activity than the unconjugated molecule and Chamow teaches bispecfic immunoadhesins (immunoglobulin fusion protein) comprising two different proteins having different functions each conjugated to a constant region of an immunoglobulin. Allegedly, one of skill in the art would have been motivated to make the claimed invention based on the teachings of these references. Applicants traverse.

MPEP §§ 2142-2143 set out criteria for establishing a *prima facie* case of obviousness for combining prior art reference teachings to arrive at the claimed invention. The Examiner's proposed combination of Davis and Chamow fails to establish a *prima facie* case of obviousness because neither of the cited references, either alone or in combination, recite all of the elements of the present claims. In addition, one of ordinary skill in the art would have lacked motivation to combine the cited references in an attempt to arrive at the claimed invention. The Examiner's assertions to the contrary represent clear legal error. In view of the Examiner's failure to establish a *prima facie* case of obviousness, Applicants request withdrawal of the rejection of record.

Applicants point out that neither Davis nor Chamow, taken alone or in combination, recite all the elements of the claims. Specifically, neither publication discloses an adzyme that is "resistant to cleavage by [its] protease domain." Chamow does not describe molecules that contain proteases. Davis mentions that proteases may be chemically-conjugated to targeting moieties, and demonstrates the use of subtilisin in one exemplary conjugate, and a lectin-directed protease in another. However, Davis does not specify that the exemplary conjugates are resistant to cleavage by subtilisin or by a lectin-derived protease. In fact, there would be no reason to engineer protease resistance into a conjugate with a lectin-directed protease, because the

conjugate does not contain lectin. Thus, Davis does not disclose a composition that is specifically described or taught as being resistant to cleavage by the protease domain.

In previous Office Actions, the Examiner agreed that Davis fails to teach resistance to the protease domain, but yet appeared to rely on an inherency argument: while Davis "did not mention the resistively to auto proteolysis, there is no available evidence to suggest that they are labile to autoproteolysis and furthermore as their fusion proteins are stable enough to show protease activity to cleave substrate polypeptide they must be inherently resistant to self cleavage" (see page 6 of Office Action dated July 25, 2007). Applicants submit that the previous arguments alleging inherency were used in support of 102(b) rejections. However, even if true, the use of inherency is not sufficient to establish a case of *prima facie* obviousness. Although inherency is often relevant in the context of anticipation, it is rarely relevant to an assessment of obviousness (*Jones* v. *Hardy,* 727 F.2d 1524 (Fed. Cir. 1984); *Adams,* 53 C.C.P.A. 996 (CCPA 1966); *Caldwell,* 50 C.C.P.A. 1464 (CCPA 1963)), for the simple reason that "[t]hat which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown" *Application of Spormann, 53* C.C.P.A. 1375,363 F.2d 444,448, 150 U.S.P.Q. (BNA) 449, 452 (1966) (citing *In re Adams,* 356 F.2d 998,53 CCPA). Thus, a combination of Davis and Chamow fails to meet each and every element of the claimed invention. This is true regardless of whether certain limitations could be inherent in the references; a point which Applicants do not concede.

Not only does the combination of Davis and Chamow lack all the limitations of the claims, but Applicants submit that one of skill lacks motivation to combine the references. Davis teaches proteins linked by chemical conjugation, but does not teach immunoglobulin fusion complexes comprising a first fusion protein bound to a second fusion protein. Further, Davis does not teach fusion proteins comprising the constant portion of an immunoglobulin heavy chain. In fact, Davis specifically teaches the benefits of using chemical conjugation, rather than using fusion proteins, because chemically coupling imparts greater flexibility in the design of the molecules. In addition, chemical coupling facilitates the use of targeting domains that may be small organic molecules or other non-protein ligands. Davis enumerates many advantages of using non-protein targeting moieties on page 21, lines 1-12. In summary, Davis specifically

teaches the advantages of using only chemical conjugation techniques, but does not lead one of skill to make fusion proteins. In fact, Davis teaches away from making fusion proteins because such fusions (i) would lack the benefits described by Davis for chemical conjugates and (ii) would be unsuitable for use in the context of non-protein targeting moieties.

Chamow does teach immunoadhesion molecules. However, there is no motivation to combine the fundamentally different teachings of Chamow with those of Davis. In fact, Davis teaches away from making such a combination because Davis specifically teaches the benefits of chemical conjugation to impart flexibility in the design of the conjugate, to create a predictable pairing between catalytic domains and targeting domain, and to facilitate conjugation to non-protein targeting moieties. These goals are not furthered (and, in fact, would be hindered) in the context of Chamow's immunoadhesion molecules. For example, forming fusion proteins with Fc domains does not permit use of non-protein targeting domains. In addition, the assembly of immunoadhesins is not a predictable union between the catalytic domain and the targeting domain. Accordingly, given that the principles underlying the teachings of Chamow undermine the goals of the chemical conjugates taught by Davis, there is no motivation to combine the teachings of Davis and Chamow.

Moreover, Applicants note that Chamow does not teach the use of a protease domain as set forth in the claims. Rather, Chamow discloses the use of an enzyme as a targeting domain. In other words, Chamow teaches that the enzyme is the targeting domain, not a protease domain. Thus, Chamow does not teach *bispecific* molecules featuring a protease domain and a targeting domain, as set forth in the claims. This further underscores that Chamow and Davis are distinct technologies, and that one of skill in the art would have no motivation to combine these technologies to arrive at the claimed invention.

The Examiner appears to have hand-picked elements of the claims from a variety of sources in the literature in order to arrive at the present claims. However, in doing so, the Examiner has failed to provide a motivation for selecting the particular combination of elements set forth in the claims. Instead, it appears that the Examiner has started from the claimed invention and then identified prior art references that recite similar words or share certain

categories of features. This is insufficient to undermine the patentability of the claimed invention. Moreover, this approach represents impermissible hindsight. MPEP 2142.

> Knowledge of applicant's disclosure must be put aside in reaching this determination, yet kept in mind in order to determine the "differences," conduct the search and evaluate the "subject matter as a whole" of the invention. The tendency to resort to "hindsight" based upon applicant's disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art.

Applicants assert that the Examiner has not established a *prima facie* case of obviousness. There is no motivation to combine the fundamentally distinct teachings of Davis and Chamow to arrive at the claimed invention. Accordingly, Applicants respectfully request withdrawal of the rejection.

Applicants take this opportunity to address another deficiency of the instant obviousness rejection. On page 8 of the Office Action, the Examiner asserted that the cited references "meets all of the structure limitations of the claimed invention and the additional limitations in claims 4, 21-22, and 30-34 appears to be intended uses of the claimed invention. Intended use limitations do not carry a patentable weight." Applicants respectfully disagree with the Examiner's conclusory statement that the limitations of claims 4, 21-22, and 30-34 are merely intended use limitations. For example, claim 4 more particularly points out the identity of the protease domain, and claims 21-22, and 30 more particularly point out the substrate for the adzyme. Given that the targeting moiety of the adzyme binds to the substrate, claim limitations that specify the substrate necessarily provide further structural description of the targeting moiety of the adzyme. Thus, dependent claims that further limit the claims by specifying features of the substrate do impart structural description to those dependent claims. Given that Applicants' dependent claims include features that are not merely statements of intended use, but rather do further limit the scope of the claims, Applicants submit that these claims must be either indicated as non-obvious or addressed as part of the Examiner's obviousness analysis. In the event that the Examiner elects to maintain the instant obviousness rejection despite the detailed arguments provided above, and in the event that the Examiner elects to apply this rejection to claims 4, 21-

22, and 30-34, Applicants submit that such a rejection should be made in a non-final Office Action.

Claim 5 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Davis in view of Chamow as applied to claims 1, 4, 19-27, 30-34 and 37 above, and further in view of Dolinar et al. (*Food tecnol and biotech.* 2000, 38, 5-9, hereinafter "Dolinar"). The Examiner asserts that Dolinar, which relates to the reversible protease inhibitor MMTS (methyl methane-thiosulfate) and refolding of a cysteine proteinase type protein, would be combined with the other references to arrive at a fusion protein complex comprising a protease using a protease inhibitor so that said fusion protein complex would not be cleaved by the protease.

Applicants respectfully traverse. As discussed above, the cited references provide no motivation for making the particular combination of elements reflected in the claimed invention. Rather, the cited references represent a hodge-podge of teachings that recite certain words that are also recited in the claims. This is not sufficient to establish a *prima facie* case of obviousness. The teachings of Dolinar do not overcome these deficiencies. If an independent claim, for example independent claim 1, is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom (e.g., claim 5) is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Accordingly, reconsideration and withdrawal of this rejection are requested.

Claims 38-40 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Davis in view of Chamow as applied to claims 1, 4, 19-27, 30-34 and 37 above, and further in view of Sanderson et al. (Medic. Res. Rev. 1999, 19, 179-197, hereinafter "Sanderson"). The Examiner asserts that Sanderson teaches a small molecule non-covalent binding protease inhibitor used in a pharmaceutical composition which is reversible and safe to humans. Allegedly, one of skill would be motivated to add such a protease inhibitor to a pharmaceutical composition comprising "an adzyme of Davis et al. and Chamow et al...as taught by Sanderson et al. to extend the shelf life of the adzyme."

As discussed above, the cited references provide no motivation of making the particular combination of elements reflected in the claimed invention. Rather, the cited references represent a hodge-podge of teachings that recite certain words that are also recited in the claims. This is not sufficient to establish a *prima facie* case of obviousness. The teachings of Sanderson do not overcome these deficiencies. If an independent claim, for example independent claim 1, is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom (e.g., claim 38-40) is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Accordingly, reconsideration and withdrawal of this rejection are requested.

Double Patenting Rejection

The Office Action states that the provisional double patenting rejection will be withdrawn upon allowance when Applicants submit a terminal disclaimer.

Applicants reiterate that, pursuant to MPEP 804, "[i]f the 'provisional' double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent [without filing a terminal disclaimer], thereby converting the 'provisional' double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent."

Applicants note that no claim has been issued in either of the co-pending application Nos. 10/792,498 and 10/650,592. Thus if the only rejection in the instant application is a provisional double patenting rejection, the Examiner should withdraw that rejection and permit the application to issue as a patent without requiring a terminal disclaimer.

If conflicting claims are first allowed in the co-pending U.S. Application No. 10/792,498 or U.S. Application No. 10/650,592, and appear in an issued U.S. patent, Applicants note that, pursuant to 37 C.F.R. § 1.130(b), a timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) may be used to overcome the double patenting rejection. Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter.

CONCLUSION

Applicants submit that the application is in condition for allowance.

The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. The Director is hereby authorized to charge any other deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. **18-1945**, from which the undersigned is authorized to draw under Order No. **COTH-P02-001**.

Dated: October 27, 2009

Respectfully submitted,

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